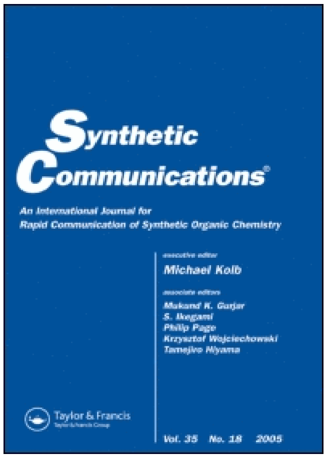

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Preparation and Deprotection of Aldehyde Dimethylhydrazones

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Preparation and Deprotection of Aldehyde Dimethylhydrazones

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Abstract: Aldehydes were conveniently protected as dimethylhydrazones by stirring a mixture of the aldehyde, N,N-dimethylhydrazine, anhydrous magnesium sulfate, and dichloromethane at room temperature. Azeotropic removal of water, formed during the course of the reaction, was not required because anhydrous magnesium sulfate functions as a water scavenger. Deprotection of aldehyde dimethylhydrazones was accomplished by stirring a mixture of the aldehyde dimethylhydrazone and aqueous glyoxylic acid at room temperature. The reaction time for the preparation and deprotection of aldehyde dimethylhydrazones varied with the structure of the aldehyde.

Keywords: Aldehyde dimethylhydrazones, aqueous glyoxylic acid, deprotection, N,N-dimethylhydrazine, prepartion

INTRODUCTION

Protection of carbonyl compounds as dimethylhydrazones is a common practice[1] that enables the synthesis of spiroacetal compounds via metalated hydrazones,[2] the conversion of aldehydes to nitriles,[3] and the

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conversion of aldehydes to α,β-unsaturated aldehydes via silyl aldehyde dimethylhydrazones.[4]

Deprotection of ketone dimethylhydrazones occurs readily under very mild conditions (e.g., wet silica gel in THF);[5] however, deprotection of aldehyde dimethylhydrazones is more difficult because nitriles can be formed by loss of dimethylamine.[3] Aldehyde deprotection conditions have been developed that rely on conversion of the aldehyde dimethylhydrazones to the methiodide and then stirring with a mixture of 5% aqueous HC1,[4] but these conditions would not be suitable for acid-labile unsaturated aldehydes. A more recent method utilized aqueous $CuCl_2$ in THF;[6] however, attempts to deprotect diene aldehyde dimethylhydrazones resulted in large amounts (about 20%) of a mixture of unknown side products. Aldehyde oximes can be deprotected by 50% aqueous glyorylic aci,[7] and investigation found that 50% aqueous glyoxylic acid could also be used to deprotect aldehyde dimethylhydrazones.

Improved methods for the preparation of aldehyde dimethylhydrazones and deprotection of aldehyde dimethylhydrazones are presented in this article (Table 1). Although existing methods for the preparation[1] and deprotection[1,6] of aliphatic or aromatic aldehyde dimethylhydrazones are usually sufficient, these methods do not work well for some unsaturated aldehyde dimethylhydrazones.

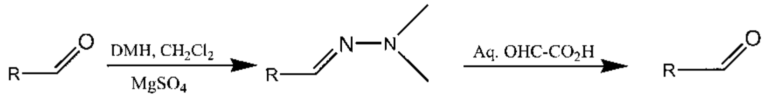
The synthetic utility of dimethylhydrazone derivatives of aldehydes, especially unsaturated ones, should be enhanced as a result of this report. Alkyl halides can be converted to aldehydes with extension of the carbon chain by two carbons with acetaldehyde dimethylhydrazone.[4] Alkylation at the α-position of 3-methyl-2-butenal dimethylhydrazone, along with double bond migration from the α,β-position to the β,γ-position, was utilized in a concise synthesis of lavandulol.[6]

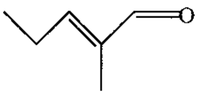
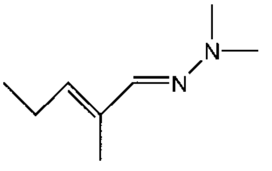
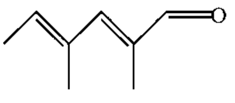
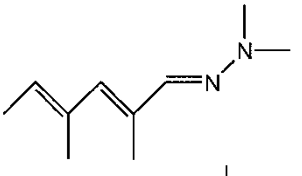
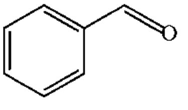
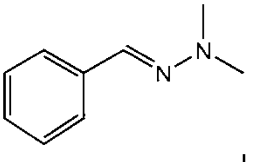
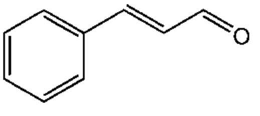
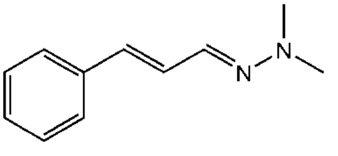
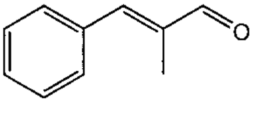
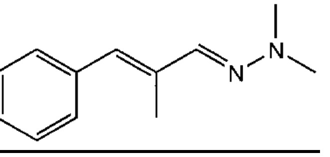
EXPERIMENTAL

Preparation of Aldehyde Dimethylhydrazones

Aldehydes were protected as dimethylhydrazones by stirring a mixture of the aldehyde (1 mmol), N,N-dimethylhydrazine (1.3 mmol), anhydrous magnesium sulfate (2 mmol), and dichloromethane (3 mL) at room temperature. After gas chromatography (GC) analysis indicated the complete conversion of starting aldehyde to product, the reaction mixture was filtered and the solvent and unreacted N,N-dimethylhydrazine were removed by rotary evaporation at water aspirator pressure to afford the aldehyde dimethylhydrazone with a purity ranging between 96% and 99%, which reflected the purity of the starting aldehyde. The only exception was the preparation of the dimethylhydrazone derivative of (2*E*,4*E*)-2,4-dimethylhexadienal, which resulted in a mixture composed of 85% of the desired product along with 15% of unreacted starting material after 96 h. The product, from a 10-mmol

Table 1. Preparation and deprotection of aldehyde dimethylhydrazones



Entry	Aldehydes	Aldehyde dimethylhydrazones
1	CH_3-$(CH_2)_6$-CHO	CH_3-$(CH_2)_6$-CH=N-N$(CH_3)_2$
2		
3		
4		
5		
6		

scale synthesis, can be easily separated from unreacted starting material by Kugelrohr distillation. After distillation, the purity of N′-(2,4-dimethyl-hexa-2,4-dienylidene)-N,N-dimethyl-hydrazine (bp 38°C at 0.05 Torr) was 98%.

Deprotection of Aldehyde Dimethylhydrazones

Deprotection was accomplished by stirring a solution containing the aldehyde dimethylhydrazone (1 mmol) and 50% aqueous glyoxylic acid (2 mL) at room temperature. The course of each reaction was followed by GC. For analysis, an aliquot of the reaction mixture (25 μL) was added to a Teflon®-lined screw-capped vial containing hexane (3 mL) and water (0.5 mL); then the resulting mixture was shaken, and the phases were allowed to separate. The hexane phase was transferred to a new vial and dried over anhydrous Na_2SO_4 before analysis by GC.

Deprotection reactions can be worked up by extraction of the previously mentioned reaction mixture, followed by extraction with petroleum ether (bp 35 to 60°C 4×2 mL), washing the combined organic phases with water (2 mL), drying over anhydrous Na_2SO_4, filtration, and removal of solvent by rotary evaporation at water aspirator pressure to afford the free aldehyde. Purity ranged from 95% to 99% and reflected the purity of the starting aldehydes brought through the protection and deprotection steps.

Analysis of Reaction Products

Deprotection yields were determined by conversion of starting material to product as measured by gas chromatography (GC) because some of the aldehyde products are volatile enough for significant loss to occur during workup. All reaction products were identified by GC/MS, and the structures of aldehyde dimethylhydrazones were additionally verified by NMR.

For monitoring reactions by GC, a Hewlett-Packard (HP) 5890 series II instrument was equipped with flame ionization detector and interfaced to a HP ChemStation data system. The oven temperature was programmed from 50 to 280°C at 10°C/min, the cool on-column inlet tracked the oven temperature, and the detector temperature was 280°C. A DB-5 capillary column (30 m × 0.25 mm, 0.25-μm film thickness, J&W Scientific, Folsom, CA) was used with 1.0-μL sample injections.

Electro-impact mass spectra (EIMS) (70 eV) were obtained with an HP 5973 MSD instrument, equipped with a splitless injector. The oven temperature was programmed from 50 to 250°C at 10°C/min; the injector temperature was 250°C, and the detector temperature was 250°C. An EC-1 capillary GC column (30 m × 0.25 mm, 0.1-μm film thickness, Alltech, Deerfield, IL) was used with 1.0-μL sample injections.

^{1}H NMR, ^{13}H NMR, and two-dimensional NMR spectra ($CDCl_3$) were obtained on a Bruker (Bellerica, MA) Avance 400 instrument. ^{1}H and 2-D homonuclear one-bond *J* coupling correlation spectroscopy (COSY) spectra were acquired at 400 MHz whereas ^{13}C and distortionless enhancement by polarization transfer (DEPT) spectra were acquired at 100 MHz. Chemical shifts are referenced to tetramethylsilane; coupling constants (*J*) are in hertz. Assignments were made with the help of ^{1}H- and ^{13}C-Predictive software[8] and a reference[9] which gave ^{1}H NMR data for similar compounds. Published ^{1}H NMR data is available[10] for compounds **4** and **5**. It is very unlikely that any of these compounds are new; however, spectral data is given because such data is very difficult to find in the older chemical literature.

Spectral Data for Aldehyde Dimethylhydrazones

N′-Octylidene-N,N-dimethyl-hydrazine (**1**)

MS (EI) m/z (%) 170 (M^+, 76), 155 (4), 141 (4), 127 (19), 113 (15), 99 (21), 86 (100), 71 (13), 60 (21), 59 (22), 44 (48). ^{1}H NMR δ 0.91 (3H, t, $J_{7-8} = 6.7$, H-8), 1.30–1.33 (8H, m, H-4–H-7), 1.50 (2H, quintet, $J_{2-3} = 7.6$ and $J_{3-4} = 7.0$, H-3), 2.25 (2H, q, $J_{1-2} = 5.3$ and $J_{2-3} = 7.6$, H-2), 2.75 (6H, s, N-CH_3), 6.72 (1H, t, $J_{1-2} = 5.3$, H-1). ^{13}C NMR δ 14.1 (C-8), 22.6 (C-7), 27.8 (C-3), 29.2 (C-4 and C-5), 31.8 (C-6), 33.1 (C-2) 43.5 (N-CH3), 141.0 (C-1).

N,N-Dimethyl-N′-(2-methyl-pent-2-enylidene)-hydrine (**2**)

MS (EI) m/z (%) 140 (M^+, 81), 125 (40), 110 (14), 96 (100), 81 (34), 67 (15), 44 (37). ^{1}H NMR δ 1.04 (3H, t, $J_{4-5} = 7.5$, H-5), 1.86 (3H, s, CH_3 at C-2), 2.23 (2H, quintet, J_{3-4}= 7.2 and $J_{4-5} = 7.5$, H-4), 2.84 (6H, s, N-CH_3), 5.59 (1H, dd, $J_{2-3} = 0.8$ and $J_{3-4} = 7.2$, H-3), 7.09 (1H, s, H-1). ^{13}C NMR δ 11.5 (C-5), 13.9 (CH_3 at C-2), 21.5 (C-4), 43.2 (N-CH_3), 133.7 (C-2 and C-3), 135.2 (C-1).

N′-(2,4-Dimethyl-hexa-2,4-dienylidene)-N,N-dimethyl-hydrazine (**3**)

MS (EI) m/z (%) 166 (M^+, 16), 151 (80), 137 (17), 121 (100), 106 (62), 79 (47), 77 (29), 53 (12), 44 (16), 39 (18). ^{1}H NMR δ 1.75 (3H, d, $J_{5-6} = 6.9$, H-6), 1.86 (3H, s, CH_3 at C-4), 2.03 (3H, s, CH_3 at C-2), 2.86 (6H, s, N-CH_3), 5.59, (1H, q, $J_{5-6} =$ 6.9, H-5), 6.01 (1H, s, H-3), 7.08 (1H, s, H-1). ^{13}C NMR δ 13.3 (CH_3 at C-2), 13.9 (C-6), 16.6 (CH_3 at C-4), 43.2 (N-CH_3), 126.2 (C-5), 129.5 (C-4), 132.8 (C-2), 133.8 (C-3), 135.9 (C-1).

N′-Benzylidine-N,N-dimethyl-hydrazine (**4**)

MS m/z (%) 148 (M^+, 100), 133, (17), 118 (19), 90 (14), 92 (10), 77 (17), 44 (11). ^{1}H NMR δ 3.01 (6H, S, N-CH_3), 7.26 (1H, t, $J_{4-5} = 7.6$ and $J_{5-6} = 7.6$, H-5), 7.29 (1H, s, H-1), 7.36 (2H, t, $J_{4-5} = 7.6$, $J_{5-6} = 7.6$, and $J_{3-4} = 7.8$, $J_{6-7} = 7.8$, H-4 and H-6), 7.62 (2H, d, $J_{3-4} = 7.8$ and $J_{6-7} = 7.8$, H-3 and H-7), ^{13}C NMR δ 43.2 (N-CH_3), 125.6 (C-3 and C-7), 127.4 (C-5), 128.5 (C-4 and C-6), 132.9 (C-1), 136.9 (C-2).

N,N-Dimethyl-N′-(3-phenyl-allylidene)-hydrazine (**5**)

MS (EI) m/z (%) 174 (M^+, 100), 159 (10), 144 (4), 130 (35), 115 (29), 104 (18), 91 (15), 77 (17), 59 (5), 44 (7), 42 (8). ^{1}H NMR δ 2.97 (6H, S, N-CH_3), 6.66 (1H, d, $J_{2-3} = 15.9$, 1 H-3), 6.99 (1H, dd, $J_{1-2} = 7.3$ and $J_{2-3} = 15.9$, H-2), 7.26 (1H, d, $J_{1-2} = 7.3$, H-1), 7.30 (1H, t, $J_{6-7} = 7.1$ and $J_{7-8} = 7.1$, H-7), 7.35 (2H, t, $J_{6-7} = 7.1$, $J_{7-8} = 7.1$, and $J_{5-6} = 8.3$, $J_{8-9} = 8.3$, H-4 and H-6), 7.45 (2H, d, $J_{5-6} = 8.3$ and $J_{8-9} = 8.3$, H-5 and H-9). ^{13}C NMR

δ 42.8 (N-CH_3), 126.2 ((C-5 and C-9), 127.4 (C-7), 127.5 (C-2), 128.7 (C-6 and C-8), 131.8 (C-3), 135.2 (C-1), 137.3 C-4).

N,N-Dimethyl-N′-(2-methyl-3-phenyl-allylidene)-hydrazine (**6**)

MS (EI) m/z (%) 188 (M^+, 100), 173 (38), 144 (44), 129 (26), 115 (58), 91 (32), 77 (7), 59 (7), 44 (11). ^{1}H NMR δ 2.18 [(3H, s, CH_3 at C-2), 2.95 (6H, s, N-CH_3), 6.58 (1H, S, H-3), 7.20, s, H-1], 7.30 (1H, m, H-7), 7.39–7.40 (4H, m, H-6, H-8 and H-5, H-9). ^{13}C NMR δ 13.4 (CH_3 at C-2), 43.1 (N-CH_3), 126.5 (C-7), 128.2 (C-5 and C-9), 129.1 (C-6 and C-8), 131.2 (C-3), 131.8 (C-2), 136.0 (C-1), 137.9 C-4).

RESULTS AND DISCUSSION

Aldehydes were conveniently protected as dimethylhydrazones (Table 1), without the need for azeotropic removal of water[11] from the reaction mixture, because anhydrous magnesium sulfate scavenges water as it is formed during the reaction. The reaction conditions are extremely mild and result in a high yield of product (Table 2) Isolated yields were at least 98% after 20 h, except the reaction of (2*E*, 4*E*)-2,4-dimethyl-2,4-hexadienal, which yielded only 85% when terminated after 4 days.

The structures of aldehyde dimethylhydrazones were verified by EIMS and NMR spectrometry. The MS data showed the expected product molecular weight and the characteristic peak at m/z 44, corresponding to the loss of the -$N(CH_3)_2$ group. The aliphatic aldehyde dimethylhydrazone, derived from octanal, showed the expected base peak at m/z 86%.[12] The ^{1}H NMR peak at δ 2.75–3.01 (6H, s) is consistent for the expected chemical shift for the $N(CH_3)_2$ protons,[8,9] and the ^{13}C NMR peak at δ 42.8–43.5 is also consistent with the expected chemical shift for the $N(CH_3)_2$ group carbons.[8]

Table 2. Preparation and deprotection of aldehyde dimethylhydrazones (DMH)[a]

Entry	Aldehyde	Yield of DMH	Deprotection yield
1	Octanal	98%, 20 h	91%, 4 h
2	(2*E*)-2-Methyl-2-pentenal	>99%, 20 h	84%, 20 h
3	(2*E*,4*E*)-2,4-dimethyl-2,4—hexadienal	85%, 96 h	94%, 30 h
4	Benzaldehyde	>99%, 20 h	93%, 4 h
5	*trans*-Cinnamaldehyde	98%, 20 h	91%, 20 h
6	*trans*-α-Methylcinnamaldehyde	>99%, 48 h	96%, 48 h

[a]See experimental for dimethylhydrazone formation and deprotection reaction conditions.

Isolated yields are reported.

Saturated aldehyde dimethylhydrazones and aromatic aldehyde dimethylhydrazones can be readily deprotected using, previously reported methodology.[1,6] A single example of each is presented in this report (octanal and benzaldehyde). The main focus of the deprotection of the more difficult and demanding unsaturated aldehyde dimethylhydrazones, for which previously reported methodology can result in the formation of significant amounts of unwanted side products.

The deprotection of aldehyde dimethylhydrazones with 50% aqueous glyoxylic acid affords the aldehydes in very high yield and greater than 95% purity (Table 2). The yield of only 84% for the deprotection of 2-methyl-2-pentenal dimethylhydrazone can be explained by loss during the removal of solvent in vacuo. A large excess of the reagent (approx 19 equiv of glyoxylic acide per 1 equiv of aldehyde dimethylhydrazone) is required for optimal deprotection. Deprotection of the dimethylhydrazone derivative of 2-methyl-2-pentenal with 4 equiv of glyoxylic acid was only 53% complete after 1 day and reached the 95% completion level after 5 days. Deprotection of the dimethylhydrazone derivative of 2-methyl-2-pentenal with 8 equiv of glyoxylic acid was only 67% complete after 1 day and reached the 99% completion level after 2 days.

Deprotection was verified by GC/MS and the MS of the deprotected aldehyde dimethylhydrazone products matched that of the starting aldehydes. Side reactions are nonexistent or minimal, even for unsaturated aldehydes. The reaction time for the formation and deprotection of aldehyde dimethylhydrazones varied with the structure of the aldehyde. The required reaction time increased as the degree of unsaturation increased (entry 1 compared with entry 2 and entry 2 compared with entry 3) and also increased when an α-methyl group was present (entry 5 compared with entry 6). These results are an improvement over the method utilizing aqueous $CuCl_2$ in THF,[6] which reported yields ranging from 56%–89%.

SUMMARY

Aldehyde dimethylhydrazones can be readily prepared in the presence of anhydrous magnesium sulfate, which scavanges water and eliminates the need for azeotropic removal of water formed during the course of the reaction. Aqueous glyoxylic acid can be used to deprotect aldehyde dimethylhydrazones in very high yield and purity. The synthetic utility of the dimethylhydrazone protective group, for the protection of aldehydes, should be broadened as a result of this research.

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